Serial No. 10/800,992
Docket No: D-2804CON2

REMARKS

Applicants are in receipt of the Office Action mailed November 16, 2007. Claims 31-50 are pending in this matter. Applicants thank the Examiner for indicating that the arguments filed July 12, 2007 were persuasive and overcame the rejections of record.

Claim 31 has been amended to indicate that the claimed ophthalmic aqueous liquid composition contains an effective amount of a preservative component selected from the group consisting of a chlorite component and a sorbate component. This amendment is supported by the specification at e.g., page 4, lines 21-24. Claims 35-37 have been amended to be consistent with the change to claim 31.

Rejections pursuant to 35 USC §102(b)

The Examiner has now rejected claims 31, 32, 39, 41-42 and 49 as being allegedly anticipated over Lipari, U..S. Patent No. 4,383,992. Lipari is drawn to water-soluble steroid compounds or complexes containing an α- or β-cyclodextrin and a steroid.

In light of the amendments to the claims, it can be seen that Lipari does not anticipate any of the pending claims. For example, Lipari does not disclose a preservative component. Nor does Lipari disclose a sulfur-containing β-cyclodextrin

component. Since all the limitations of a claim must be present in an anticipating reference and Lipari does not disclose all the limitations of any claim now pending, applicants respectfully submit that this rejection is now moot.

Rejections Pursuant to 35 U.S.C. 103(a)

Claims 31-50 were rejected as allegedly obvious over the Lipari '992 U.S. Patent in view of Dziabo et al., U.S. Patent No. 5,424,078. Applicants respectfully traverse this rejection for the following reasons.

Lipari has been discussed; Lipari is silent with respect to preservatives or sulfur-containing derivatives of β-cyclodextrin. Dziabo et al. is drawn to the use of stabilized chlorine dioxide in aqueous ophthalmic formulations.

Neither Lipari nor Dziabo discuss or disclose the particular problems associated with formulating a preservative in a cyclodextrin-containing solution. Moreover, neither reference discloses or suggests sulfur-containing β-cyclodextrin derivatives.

The present invention is the result of a discovery made by the present inventors when they attempted to make a preserved composition containing an active agent and a cyclodextrin. When the most commonly used ophthalmic preservative benzalkonium chloride (BAK) was added to a cyclodextrin-containing solution at a concentration known to be effective in other ophthalmic

formulations it was found that BAK was ineffective as a preservative unless the concentration was significantly increased.

Applicants have since become aware of U.S. Patent No. 5,985,310, issued November 16, 1999, which is now being included with this response in a Supplemental Information Disclosure Statement for the Examiner's convenience. This reference discloses that interactions between commonly used preservatives and cyclodextrins can present "special problems"; for example "the antimicrobial activity of the preservative [including chlorobutanol, methylparaben, and propylparaben] can be reduced by the formation of preservative-cyclodextrin inclusion complexes" and "cyclodextrins can inactive the antimicrobial activity of certain quaternary ammonium compounds." '310 patent, column 1, lines 37-58.

Unlike the present specification, the '310 patent does not disclose that BAK is ineffective at commonly used concentrations in ophthalmic colution with a cyclodextrin.

The data included in the present patent application discloses that BAK is "relatively ineffective at typical concentrations in compositions containing cyclodextrin components", and thus has a reduced preservative efficacy in the presence of a cyclodextrin component. See e.g., Specification, page 3, lines 11-20. As shown in Examples 3-9 and 10-15, BAK fails to effectively preserve a solution containing a β-cyclodextrin according to U.S. Preservative Efficacy Test

(USPET) standards, even when used at the high concentration of 0.15% (w/v) (1500 ppm).

The present inventors were therefore surprised to discover that the presence of cyclodextrin did not adversely affect the preservative efficacy of two antimicrobial agents: chlorite components and sorbate salts. This finding was completely unexpected and unpredictable in light of the BAK data.

These results are summarized in the specification. Thus, Examples 16-21 of the present specification show that, unlike BAK, stabilized chorine dioxide effectively preserves a solution containing prednisolone acetate and a β-cyclodextrin at a concentration of 0.0075% (w/v) (75 ppm). Similarly, examples 30-33 demonstrate that a prednisolone acetate solution in β cyclodextrin is effectively preserved according to USPET standards with 75ppm stabilized chlorine dioxide and with 0.5% potassium sorbate. Indeed, the sorbate component permitted the solution to also pass the European Efficacy Test EPA or EPB when the pH was reduced to the acidic range.

It is therefore clear that these results, when compared to the results for the standard preservative BAK, could not have been anticipated and were utterly unpredictable. Nothing in Lipari or Dziabo would lead the person of ordinary skill in the art to believe that the antimicrobial efficacy of BAK would be affected any differently than the antimicrobial efficacy of stabilized chorine dioxide or sorbate in the presence of a

cyclodextrin. Indeed, neither Lipari or Dziabo even contemplates the use of a sorbate component as a preservative.

The non-obviousness of the present claimed invention is supported by the United States Supreme Court's recent decision in *KSR Intern. Co. v. Teleflex Inc.*, __ U.S. __, 127 S. Ct. 1727 (2007) (2007). This decision, which affirmed the vitality of the controlling case of *Graham v. John Deere, Inc.*, 383 U.S. 1 (1966), indicated that a combination is non-obvious when the result of combining the elements is unpredictable. In explaining *United States v. Adams*, 383 U.S. 39 (1969), the KSR Court indicated that "[t]he fact that the elements work[] together in an unexpected and fruitful manner support[] the conclusion that Adam's design was not obvious to those skilled in the art."

Exactly as was true in Adams, the present invention is drawn to subject matter that involve the combining of components (cyclodextrins and preservatives) in a manner that was unexpected. The person of ordinary skill in the art would have been aware in light of Castillo, U.S. Patent No. 5,985,310 that "special problems" exist in preserving cyclodextrin compositions. Castillo found that the addition of borate augmented the perservantive efficacy of benzalkonium halide compounds, and quaternary ammonium compounds. The present invention does not require borate to augment the preservative efficacy of the chlorite or sorbate preservatives.

In light of the state of the prior art (including Lipari and Dzaibo) at the time of the present invention, the person of ordinary skill in the art could therefore not have predicted that the presently claimed compositions would have sufficient preservative efficacy to pass the United States Preservative Efficacy Test. This result is therefore both "unexpected and fruitful" and, as stated by the KSR court, these facts support the conclusion that the presently claimed invention was not obvious to those skilled in the art at the time the invention was made.

Claim 40 was rejected as allegedly obvious over Lipari and Loftsson. Lipari is said to disclose prednisolone acetate and a cyclodextrin. Loftsson is said to teach sulfobutylether β-cyclodextrin in combination with a steroid.

Neither Lipari nor Loftsson appear to teach the use of specific preservatives; Loftsson states that "preservatives" may also be present, but "most preferably the ophthalmic composition is a sterile, isotonic, buffered aqueous solution", and therefore not preserved at all. '954 patent, column 19, lines 30-31.

Therefore, claim 40, which is drawn to an ophthalmic, aqueous liquid composition suitable for topical application to an eye comprising an aqueous liquid, a therapeutically effective amount of prednisolone acetate and a sulfobutyl ether β-cyclodextrin, and an effective amount of a preservative component selected from the group consisting of a chlorite component and a sorbate component, the ophthalmic composition being present as a solution, is not in

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any way rendered obvious by Lipari and Loftsson.

CONCLUSION

For the above reasons Applicants submit that the claims hare in condition for allowance and respectfully request that the Examiner issue a notice to that effect. While this reply is being submitted benfor e the expiration of the shortened statutory period (February 16, 2008), if any fee is due Applicants hereby authorize the Commissioner to use Deposit Account 01-0885 for the payment of any fee now due in connection with this communication.

Respectfully submitted,

Carlos A. Fisher
Attorney for Applicant
Reg. No. 36, 510
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (494) 450-1764